09/763308

PCT/SE00/01592

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 May 2001 (08.05.01)	
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International filing date (day/month/year) 21 August 2000 (21.08.00)	**Priority date** (day/month/year) 24 August 1999 (24.08.99)
Applicant ARVIDSSON, Per-Ola et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 March 2001 (02.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
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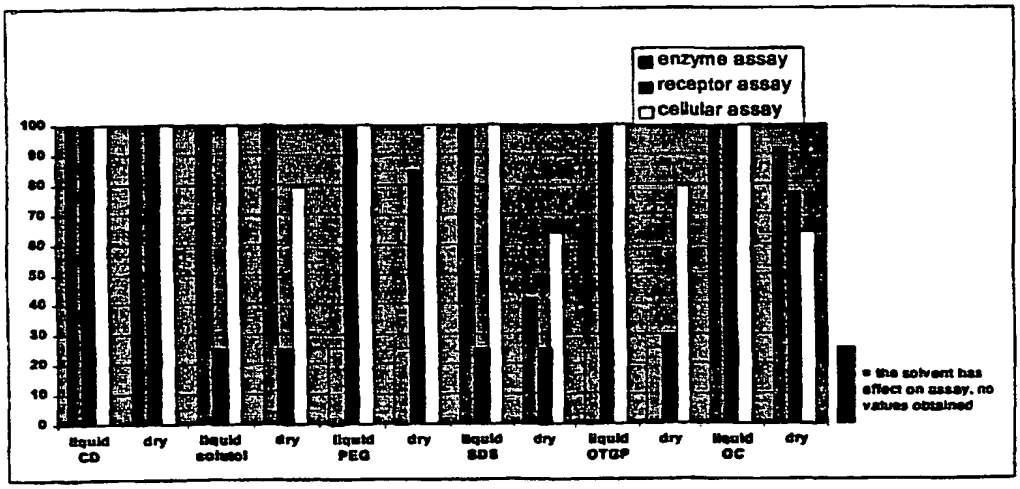
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF CYCLODEXTRIN FOR PROTECTIVE STORAGE OF CHEMICAL COMPOUND LIBRARIES



(57) Abstract: The invention relates to cyclodextrin as a protective agent for compounds in compound libraries, particularly for use in screening the compound library for biological activity. A particular advantage is improved recovery of potential activity of compounds within the library when the compounds have dried on storage.

WO 01/14291 A1

USE OF CYCLODEXTRIN FOR PROTECTIVE STORAGE OF CHEMICAL COMPOUND LIBRARIES

The invention relates to cyclodextrin as a protective agent for compounds in compound libraries, particularly for use in screening the compound library for biological activity.

High Throughput Screening (HTS) is a process in which up to many thousands or more of chemical compounds are assayed in search of biological (or other) activity. Large libraries of chemical compounds are valuable assets of research organisations. Compound libraries are used in the search for agents with novel pharmaceutical, agrochemical or other fine chemical applications and are a valuable source of structural and chemical diversity used in identifying new leads as potential inhibitors of a particular target. Compound libraries may for example contain more than 100,000 different compounds and due to increasingly efficient compound acquisition, either through commercial sources, or by high throughput synthesis, compound libraries with more than 1 million different compounds are now of a typical size in some research organisations. There is a vast variety of targets, and an even greater variety of assay methods. The goal of HTS is to identify "actives", compounds that affect the target in some manner. There are a number of problems set out below which presently hinder the optimal operation of HTS.

The compounds available for testing are called the compound library. The compounds may be hydrophilic, lipophilic, reactive or light-sensitive. The compounds are stored in solution, usually DMSO or a mixture of DMSO and water, to be available for screening. The storage is long-term (e.g. up to 5 years) and the environmental conditions are very variable. Because of the large variety of properties in the compound library, the conditions for storage can not be adjusted to individual compounds and compromises are made to suit most of the compounds and the screening process. For the screening process, the individual compounds are transferred to reaction vessels (e.g. microtitre plates) in small (e.g. sub-microliter) quantities. For performing a biological assay, the compounds are diluted in aqueous solution while adding the biological material, for example enzymes, cells or membranes. A signal is measured, representing the individual biological activity of the compound on that particular target, usually relative to a control (e.g. the biological reaction without compounds).

Compromising on storage conditions and the choice of suitable solvent may disqualify many compounds even before they reach the biological assay system. Furthermore, even more compounds may never reach the biological target, because the addition of aqueous solution

causes precipitation of molecules. There is currently no solution to this problem. Progress in screening technology i.e. moving into much smaller assay-volumes reveals another problem. Pipetting of sub-microliter quantities of chemical compounds is now possible, but it is very hard to keep the compounds solubilized, because the solvent rapidly evaporates. Most compounds are not easily resolubilized in aqueous solution once the organic solvent has evaporated and consequently the compound is not available to the biological target. The compromize of diluting in aqueous solution prior to the assay leaves one with the problem of precipitation.

High throughput multiple parallel synthesis (HTMPS) can generate very large numbers of individual compounds, typically 100-5000 per week, but the sample size is usually small, <100mg. Compounds from HTMPS are stored sometimes as dry films or as solutions, usually in dimethyl sulphoxide (DMSO). The dispensing of compounds stored as dry films is often very difficult, and the difficulty increases significantly as the sample size decreases. Compounds stored as solutions can be dispensed quickly and accurately, but some samples are unstable in solution and decompose on prolonged storage, even at low temperatures.

Increasingly the demands of a compound collection are changing. With the advent of high throughput screening (HTS) a whole compound collection of , for example, 100,000 compounds may be screened in a number of days against a new biological target, using automated or semi-automated procedures. Faced with the need for more rapid dispensing of compounds from the compound collection, the small sample size needed and the large numbers of different sample types existing in a compound collection, current systems of storage and dispensing are increasingly incompatible with modern needs.

Much of the developing new technology in drug discovery is focussing on miniaturisation. Along with many big advantages offered by miniaturisation technologies, come the problems of compounds drying out of solution (due to the evaporation of sub-microlitre volumes of solvent) and exposure of compound solutions to aqueous conditions before the screening (which can lead to precipitation of the compounds out of solution). These problems could prevent the screening of many compound classes, and therefore restrict the benefit of HTS in discovering compounds with useful biological activity.

After the priority date of the present invention, a European patent application from Evotec BioSystems GmbH published on 6Oct1999 as EP 947820. This Evotec publication includes use of cyclodextrins as additives for compound storage.

The present invention is based on the discovery that cyclodextrins can be used as a universal additive to compounds in a compound library to overcome at least some of the problems set out above.

According to one aspect of the present invention there is provided a compound library wherein each compound within the library is stored in the presence of a cyclodextrin. The number of compounds in a compound library which may be stored by the techniques as described herein is not limited by the invention, ideally the invention may be used for storage of compounds in compound libraries where the number of different compounds stored is more than 100, preferably more than 300, preferably more than 10^3, preferably more than 3000, preferably more than 10^4, preferably more than 30000, preferably more than 10^4 ,preferably more than 10^5, especially more than 10^6. Addition of compounds to the library that do not contain cyclodextrin is intended to be within the scope of the present invention provided the library sizes set out above are met with compounds that do contain cyclodextrin.

Preferred compounds are those stored in compound libraries of pharmaceutical, biotechnology or agrochemical companies. Preferred compounds are organic molecules of molecular weight of less than 2000 Daltons, and especially of 1000 Daltons or less.

Preferably the compounds within the library are selected from at least 3 chemical classes, more preferably at least 5 chemical classes, more preferably at least 7 chemical classes, more preferably at least 10 chemical classes, more preferably at least 30 chemical classes and especially at least 100 chemical classes. Examples of chemical classes include: acidic, basic and neutral compounds; aliphatic, aromatic and heteroaromatic compounds; carboxylic acids, sulphonic acids, esters, acid halides, amides, amidines, nitriles, aldehydes, ketones, alcohols, phenols, thiols, hydroperoxides, amines, imines, ethers, sulphides and peroxides; and any suitable combination or combinations thereof.

Preferably the cyclodextrin is present at a substantially uniform concentration across the library. A preferred concentration of cyclodextrin is 20-200mM, more preferably at 30-150mM, more preferably at 40-80mM and especially at 45-60mM, and especially at about 50 mM. It will be appreciated that these concentrations refer to the initial concentration upon preparation of a compound for addition to the library and that, over time, the concentration

may increase due to evaporation. It will also be appreciated that for this reason, even when one concentration of cyclodextrin is selected initially, there may be variable concentrations present in the compound library depending on differences in storage time (and therefore extent of evaporation) for individual compounds. Compounds may be purposefully dried before storage or alternatively stored in wet form and natural evaporation (if any) allowed to occur on storage. The Evotec publication states that the compounds must be stored dry (see para 18 of Evotec and the claims).

For the sake of comparison with Evotec, the reader is referred to the following parts thereof which state certain additive concentrations.

para 24: hydroxypropyl-β-CD concentrations of 0.05-4% by weight, 0.05-2% and 0.1-1.5%

Example 1: hydroxypropyl-β-CD concentration of 1.5%.

Example 2: hydroxypropyl-β-CD concentration of 0.1%.

A comparison of concentration units is presented below.

hydroxypropyl-β-CD concentration (mM)	hydroxypropyl-β-CD concentration (% by weight)
20-200	2.8-28
30-150	4.2-21
40-80	5.6-11.2
45-60	6.3-8.4
50	7

Therefore the stated additive concentrations herein are novel over Evotec.

One cyclodextrin or a mixture of cyclodextrins may be used, either within a single compound or across the library as a whole. An especially preferred cyclodextrin is 2-hydroxypropyl-b-CD.

According to another aspect of the present invention there is provided a method of preparing a compound library of the invention which comprises the addition of a cyclodextrin to each compound within the library. In one embodiment, the library may be stored in wet form.

According to another aspect of the present invention there is provided a method of screening a compound library of the invention which comprises assay of at least 100

compounds from the library in the presence of a cyclodextrin. Preferred assays include enzyme, receptor and cellular models.

The addition of CDs to compound libraries solves at least some of the problems faced with known compound libraries as described above. For example, we have discovered that many structurally different compounds within a compound library are protected against degradation and oxidation in the presence of CDs and they can be widely used to enhance solubility of molecules in aqueous solution. Furthermore compounds can be dried in the reaction vessel without loosing their biological activity. CD has not yet shown any effects on the biological systems tested: no inhibition or activation due to the CDs could be shown, and no side-effects on signal-detection have been observed so far. Furthermore, CD has not yet shown any negative effects on compound availability in any tested bioassay.

Without wishing to be bound by theoretical considerations, we believe that some of advantages of the invention may be due, at least in part, to the following properties of CDs. CDs are capable of forming inclusion complexes with drug molecules by taking up the molecules in their cavity. The inclusion complex is in equilibrium with the surrounding environment of water molecules, CD-molecules and free drug molecules. The compounds are readily released from the inclusion complex by dilution in aqueous solution, i.e displacing the equilibrium in favour of the free molecules. Formation and dissociation of the inclusion-complex is a rapid process, usually only minutes. For very hydrophobic compounds the equilibrium is first reached after hours or days. CDs are not only used to enhance solubility but also to stabilize compounds both in dry formulations and in solutions. CDs can prevent compounds from hydrolysis, oxidation and also photodestruction by protecting them from a potentially reactive environment. Cyclodextrins have been reviewed by Jozsef Szejtli in Chem. Rev. (1998), **98**, 1743-53.

Abbreviations

CD	cyclodextrin
DMSO	dimethylsulphoxide
2-HP-CD	2-hydroxypropyl-b-cyclodextrin
HTMPS	high throughput multiple parallel synthesis
HTS	high throughput screening
OC	octylcycloside
OTGP	octylthioglucopyranoside
PEG	polyethyleneglycol
SDS	sodium dodecyl sulphate

The invention will now be illustrated by the following non-limiting Examples in which:

Figure 1 shows the percentage of compounds retaining their biological activity after different treatments compared with the initial number of biologically active compounds (actives) in DMSO-solution. The compounds were dissolved in DMSO, water or cyclodextrin (40 mM) in DMSO, and used either in liquid or after the liquid has evaporated (dry). Three different assay-methods were used: *Enzyme assay*: Enzyme activity was monitored in an aqueous buffer system by absorbance changes. *Receptor assay:* binding of isotopically labelled ligand to membrane preparations in an aqueous buffer system was measured by scintillation. *Cellular assay:* A functional cell response was monitored after induction in aqueous medium by luminescence measurement.

Figure 2 shows the percentage of compounds retaining their biological activity after different treatments compared to the initial number of biologically active compounds (actives) in Cyclodextrin-DMSO-solution (40mM). The compounds were dissolved in Solutol™-DMSO (0.1 mM), Polyethyleneglycol-DMSO (20%), SDS-DMSO (20 mM), Octyl-Thioglucopyranoside-DMSO (20 mM) and Octylcycloside-DMSO (50 mM) and used either in liquid or after the liquid has evaporated (dry). Solutol™ is sold by BASF as nonionic solubilizer in paste form for use in human and veterinary injections and is described in the BASF catalogue as "Solutol HS 15: macrogol-15 hydroxystearate produced by reacting 15 moles of ethyl oxide with 1 mole of 12-hydroxystearic acid". The same assays as in Example 1 were used.

Example 1

Compound accessibilty after drying and aqueous dilution.

A selection of 80 compounds of known biological activity and poor aqueous solubility were screened in 3 different biological systems (enzyme and receptor binding assays), in the presence and absence of cyclodextrin (40mM 2-HP-CD) in the organic solvent.

The enzyme assay was a peroxidase assay with a chromogenic substrate. The receptor assay was a G-protein coupled receptor assay performed as SPA™ (Amersham, scintillation proximity assay technology) with a membrane preparation linked to scintillant beads and a radiolabelled ligand. The cellular assay was a cytokine stimulated monocyte cell-line providing a measurable luminescent response.

The compounds were exposed to drying conditions and aqueous dilution (conditions which can cause precipitation of the compounds), and then tested in the biological assays, in a manner equivalent to the standard HTS process. The results are shown in Figure 1.

The findings are as follows:

Increased solubility in aqueous solutions, more compounds stay in solution without precipitating, resulting in more active compounds identified.

Conserved biological activity after drying in the reaction vessel: compounds that have shown activity on a certain target loose that activity if the compound dried out due to DMSO evaporation prior to the biological assay. When CD is present those active compounds keep their activity also after being dried.

Several effects were demonstrated:

- Cyclodextrin itself did not affect the normal functioning of the biological assays tested.
- In the absence of cyclodextrin the drying conditions of the compounds cause loss of all or most of the biological activities caused by the compounds
- In the presence of cyclodextrin all of the known biological activities of the compounds were retained after the drying treatments.

Example 2

HTS experiments with 1600 compounds

1600 different compounds screened in the presence and absence of cyclodextrin (2-HP-CD, 50 mM). These experiments provided further confirmation of the preliminary

observations, although this time with a larger number of compounds, not pre-selected for low solubility properties. The results were not as clear-cut as in the preliminary trials, but still very promising.

Firstly, the cyclodextrin did not adversely affect the biological assays, in common with the first trials. Further, it generally revealed more biological activity of the compounds than was seen without cyclodextrin after drying or aqueous dilution treatments, which could otherwise result in compound loss by precipitation.

Several effects were demonstrated:

Increased bioavailability of compounds for the target: Molecules that did not show activity in the absence of CD, can become active because the bioavailability is improved by CD, making for example lipophilic compounds soluble in aqueous solution.

Increased solubility in aqueous solutions, more compounds stay in solution without precipitating, thus resulting in more active compounds

Conserved biological activity if it is necessary to dilute compounds in aqueous solution prior to the asssay: compounds that have shown activity on a certain target may loose that activity due to precipitation if the compound is diluted in aqueous solution prior to the assay. When CD is present those compounds mostly keep their activity because precipitation is prevented.

Comparative Example 1

Comparison of Cyclodextrin with other possible protective agents

The same experimental setup as in Example 1 was used to compare the performance of cyclodextrin with other potential protective agents. None of the other agents showed the advantageous properties (e.g. biologically inert, protective in dry conditions) as well as cyclodextrin; see Figure 2.

The conclusion was that CD was by a large margin the best protective agent tested.

Claims

1 A compound library wherein each compound within the library is stored in the presence of a cyclodextrin wherein the cyclodextrin concentration is 20-200mM.

2 A compound library according to claim 1 comprising at least 1000 compounds.

3 A compound library according to claim 1 comprising at least 10000 compounds.

4 A compound library according any preceding claim wherein the compounds are organic molecules of molecular weight of less than 2000 Daltons.

5 A compound library according to claim 4 wherein the compounds are organic molecules of molecular weight of less than 1000 Daltons.

6 A compound library according to any preceding claim wherein the cyclodextrin concentration is 30-150mM.

7 A compound library according to any preceding claim wherein the cyclodextrin concentration is 40-80mM.

8 A compound library according to any preceding claim wherein the cyclodextrin concentration is 45-60mM.

9 A compound library according to any preceding claim wherein the cyclodextrin concentration is 50mM.

10 A compound library according to any preceding claim wherein the cyclodextrin is 2-hydroxypropyl-b-cyclodextrin.

11 A compound library according to any preceding claim in wet form.

12 A method of preparing a compound library as defined in any of claims 1-11 which comprises the addition of a cyclodextrin to each compound within the library and storage of the compound library in wet form.

13 A method of screening a compound library as defined in any of claims 1-11 which comprises assay of at least 100 compounds from the library.

14 A method according to claim 13 in which the assay is selected from the group consisting of enzyme assay, receptor assay and cellular assay.

Figure 1

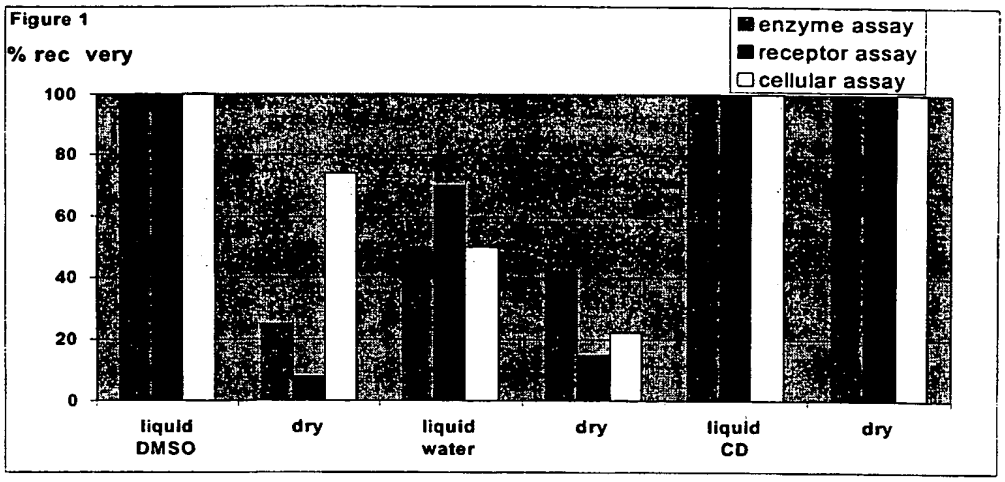
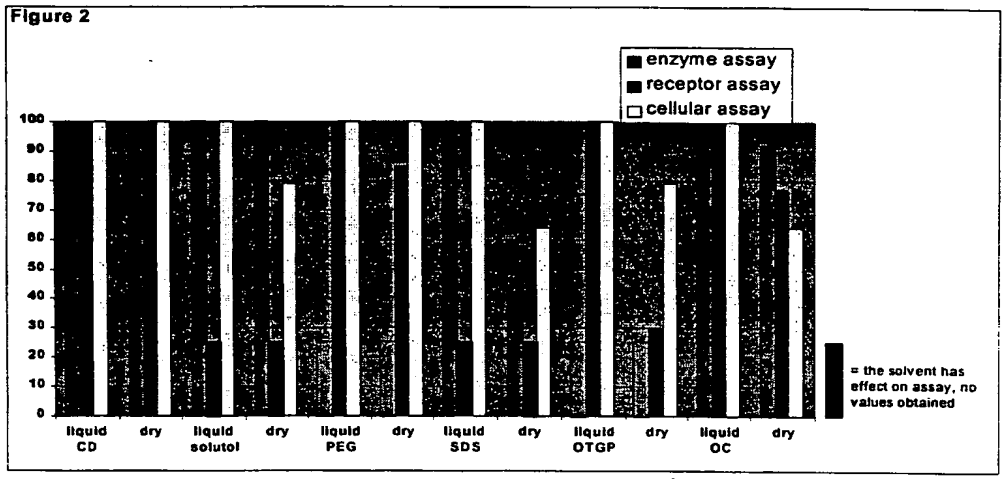


Figure 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01592

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07B 63/04 // C08B 37/16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0947820 A2 (EVOTEC BIOSYSTEMS GMBH), 6 October 1999 (06.10.99) --	1-10,13,14
X	EP 0609766 A2 (NISSHO CORPORATION), 10 August 1994 (10.08.94) --	1-3,6-9, 11-14
A	US 5580856 A (STEVEN J. PRESTRELSKI ET AL), 3 December 1996 (03.12.96) --	1-14
A	WO 8502767 A1 (JANSSEN PHARMACEUTICA N.V.), 4 July 1985 (04.07.85) --	1-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual c mpletion of the international search	Date of mailing f the international search report
7 December 2000	1 1 -12- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile N . +46 8 666 02 86	Authorized officer Hampus Rystedt/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01592

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. Rev., Volume 98, 1998, Józef Szejtli, "Introduction and General Overview of Cyclodextrin Chemistry" page 1743 - page 1753 -- --------	1-14

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 00/01592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0947820 A2	06/10/99	NONE	
EP 0609766 A2	10/08/94	SE 0609766 T3	
		DE 69417600 D,T	02/09/99
		ES 2129531 T	16/06/99
		JP 6281653 A	07/10/94
		US 5441879 A	15/08/95
US 5580856 A	03/12/96	NONE	
WO 8502767 A1	04/07/85	AT 51145 T	15/04/90
		AU 565966 B	01/10/87
		AU 3835285 A	12/07/85
		CA 1222697 A	09/06/87
		CY 1689 A	14/01/94
		DE 3346123 A	27/06/85
		DE 3481680 D	00/00/00
		DK 359585 A	07/08/85
		EP 0149197 A,B	24/07/85
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		FI 86140 B,C	15/04/92
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		HK 131293 A	03/12/93
		HU 40561 A	28/01/87
		JP 5070612 B	05/10/93
		JP 61500788 T	24/04/86
		KR 9208700 B	08/10/92
		LU 90283 A	03/11/98
		NO 171888 B,C	08/02/93
		NO 853070 A	02/08/85
		SG 24893 G	06/08/93
		ZA 8410042 A	25/09/85

PATENT COOPERATION TREATY

09/763308

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D 2234-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/01592	21/08/2000	24/08/1999
International Patent Classification (IPC) or national classification and IPC C07B63/04		
Applicant ASTRAZENECA AB et al.		

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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/03/2001	13.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Butkowskyj-Walkiw, T Telephone No. +49 89 2399 8594

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE00/01592

I. Basis of th r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-8 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

V.

In the light of the documents cited in the search report the present claims 1-14 can be considered as being novel (Art. 33(2) PCT).
However, in the light of D1 (EP-A-0 609 766; claims 1-5; pages 2,3) the present claims 1-14 cannot be considered as being inventive (Art. 33(3) PCT) as the object of the present application, namely to provide a protective agent for compounds in compound libraries, particularly for use in screening the compound library for biological activity, has already been suggested by said document.

VI.

The present application claims priority rights from 31/8/99. The priority document pertaining to the present application was not available at the time of estabilishing this report. The current assessment is based on the assumption that the present priority is validly claimed. EP-A-0 947 820, cited in the search report is therefore not considered art of the prior art for the purposes of Art. 33(2)(3) PCT pursuant to Rule 64(3) PCT.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* D 2234-1 WO

Box No. I TITLE OF INVENTION

CHEMICAL COMPOUNDS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AstraZeneca AB
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.
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Facsimile No.
+8 553 288 20

Teleprinter No.

State *(that is, country)* of nationality:
SE

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ARVIDSSON, Per-Ola
AstraZeneca R&D Lund
S-221 87 Lund
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
SE

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Global Intellectual Property, Patents
AstraZeneca AB
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Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DIVERS, Mark
AstraZeneca R&D Lund
S-221 87 Lund
Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PETERSEN-MAHRT, Silja
AstraZeneca R&D Lund
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Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AE** United Arab Emirates
- ☒ **AG** Antigua and Barbuda
- ☒ **AL** Albania .....
- ☒ **AM** Armenia .....
- ☒ **AT** Austria .....
- ☒ **AU** Australia .....
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina .....
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria .....
- ☒ **BR** Brazil .....
- ☒ **BY** Belarus .....
- ☒ **BZ** Belize
- ☒ **CA** Canada
- ☒ **CH and LI** Switzerland and Liechtenstein
- ☒ **CN** China .....
- ☒ **CR** Costa Rica .....
- ☒ **CU** Cuba .....
- ☒ **CZ** Czech Republic .....
- ☒ **DE** Germany .....
- ☒ **DK** Denmark .....
- ☒ **DM** Dominica
- ☒ **DZ** Algeria .....
- ☒ **EE** Estonia .....
- ☒ **ES** Spain .....
- ☒ **FI** Finland .....
- ☒ **GB** United Kingdom
- ☒ **GD** Grenada
- ☒ **GE** Georgia .....
- ☒ **GH** Ghana .....
- ☒ **GM** Gambia
- ☒ **HR** Croatia .....
- ☒ **HU** Hungary .....
- ☒ **ID** Indonesia
- ☒ **IL** Israel .....
- ☒ **IN** India .....
- ☒ **IS** Iceland
- ☒ **JP** Japan .....
- ☒ **KE** Kenya .....
- ☒ **KG** Kyrgyzstan .....
- ☒ **KP** Democratic People's Republic of Korea .....
- ☒ **KR** Republic of Korea .....
- ☒ **KZ** Kazakhstan .....
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho .....
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MA** Morocco .....
- ☒ **MD** Republic of Moldova .....
- ☒ **MG** Madagascar .....
- ☒ **MK** The former Yugoslav Republic of Macedonia .....
- ☒ **MN** Mongolia
- ☒ **MW** Malawi .....
- ☒ **MX** Mexico .....
- ☒ **MZ** Mozambique
- ☒ **NO** Norway
- ☒ **NZ** New Zealand .....
- ☒ **PL** Poland .....
- ☒ **PT** Portugal .....
- ☒ **RO** Romania
- ☒ **RU** Russian Federation .....
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia .....
- ☒ **SK** Slovakia .....
- ☒ **SL** Sierra Leone .....
- ☒ **TJ** Tajikistan .....
- ☒ **TM** Turkmenistan .....
- ☒ **TR** Turkey .....
- ☒ **TT** Trinidad and Tobago .....
- ☒ **TZ** United Republic of Tanzania
- ☒ **UA** Ukraine .....
- ☒ **UG** Uganda .....
- ☒ **US** United States of America .....
- ☒ **UZ** Uzbekistan .....
- ☒ **VN** Viet Nam .....
- ☒ **YU** Yugoslavia .....
- ☒ **ZA** South Africa .....
- ☒ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application receiving Office
item (1) 24 August 1999 (24.08.1999)	9902988-6	Sweden		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date (day/month/year)	Number	Country (or regional Office)
6 April 2000	SE99/01107	Sweden

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 8
claims	: 1
abstract	: 1
drawings	: 1
sequence listing part of description	:
Total number of sheets	: 15

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: GF1189/2000
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: ITS Report SE99/01107

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 21 August 2000

Christer Wahlström
Global Intellectual Property, Patents, AstraZeneca AB

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau: